PATENT COOPERATION TREATY

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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18 SEP 2000
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2. NS
3.

PCT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing (day/month/year): 15 SEP 2000

Applicant's or agent's file reference
FP11522

IMPORTANT NOTIFICATION

International application No.	International filing date	Priority date
PCT/AU99/00812	24 September 1999	25 September 1998

Applicant
THE UNIVERSITY OF QUEENSLAND et al

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translations to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide

Name and mailing address of the IPEA/AU

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference FP11522	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416).
International application No. **PCT/AU99/00812**	International filing date *(day/month/year)* 24 September 1999	Priority Date *(day/month/year)* 25 September 1998
International Patent Classification (IPC) or national classification and IPC **Int. Cl.** [7] C07K 1/02, 1/04, 1/107		
Applicant THE UNIVERSITY OF QUEENSLAND et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 3 sheets, including this cover sheet.

   [X] This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 5 sheet(s).

3. This report contains indications relating to the following items:

I	[X]	Basis of the report
II	[ ]	Priority
III	[ ]	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	[ ]	Lack of unity of invention
V	[X]	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	[ ]	Certain documents cited
VII	[ ]	Certain defects in the international application
VIII	[ ]	Certain observations on the international application

Date of submission of the demand 29 March 2000	Date of completion of the report 11 August 2000
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized Officer S.R. IDRUS Telephone No. (02) 6283 2536

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/AU99/00812

I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed.

☒ the description, pages **1-12, 14-69** as originally filed,
pages , filed with the demand,
pages **,13** received on **1 August 2000** with the letter of **1 August 2000**

☒ the claims, pages **,73 , 75-77** as originally filed,
pages , as amended (together with any statement) under Article 19,
pages , filed with the demand,
pages **,70-72, 74** received on **1 August 2000** with the letter of **1 August 2000**

☒ the drawings, pages **1/2 -2/2,** as originally filed,
pages , filed with the demand,
pages , received on with the letter of

☐ the sequence listing part of the description:
pages , as originally filed
pages , filed with the demand
pages , received on with the letter of

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, was on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages

☐ the claims, Nos.

☐ the drawings, sheets/fig.

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report*

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-34	YES
	Claims		NO
Inventive step (IS)	Claims	1-34	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-34	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

The International Search report cited the following documents;
D1 Chemical Abstracts 131:10019,
D2 Chemical Abstracts 126:235027,
D3 Chemical Abstracts 108:90453,
D4 Chemical Absracts 92:17693,
D5 Chemical Abstracts 82:98387,
D6 Derwent abstract Accession No.96-189114/20,

D1 disclosed amino acids linked at their N-termini to cis-amino indenol and trans-diaminocylohexane, compounds which fall within the scope of the auxiliary compounds of General Formula I (cf. claims 1 and 11). See also compounds 1-16 disclosed. However, because the present claimed subject matter is entitled to its priority date and **D1** being an intermediate non-patent literature document it is not novelty destroying.

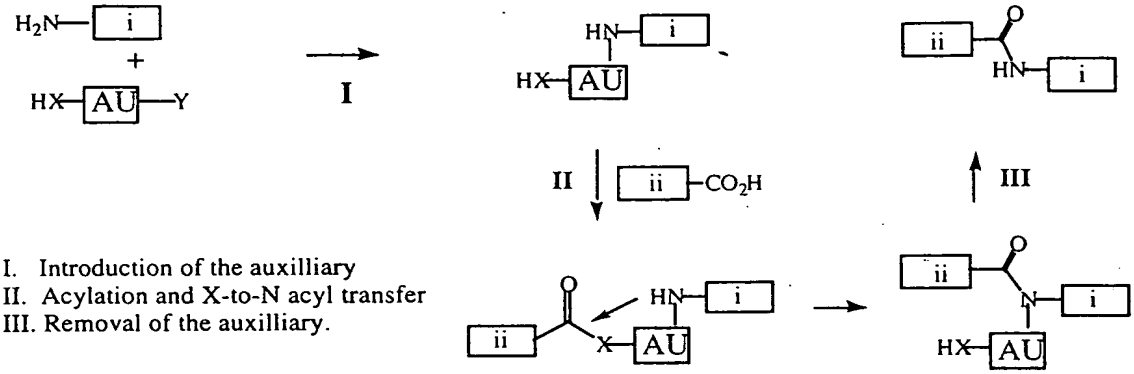
D2 disclosed catalytic antibodies selected from antibody library. See Figures 1 and 3.
D3 disclosed the linking of enzymes with 5-nitrosalicyaldehyde.
D4 disclosed the linking of 4-methoxy-2-naphthylamine with 5-nitrosalicyladehyde
D5 disclosed the coupling of a number of pepetides with 2-ethyl benzisoxazolium fluoborates. See Table 7.
D6 disclosed the coupling of peptides and proteins to high affinity chelates of formulae I, II, and III. See page 3 line 4-11 and page 22).

However, none of these references disclose or suggest the use of the linked compound in order to facilitate the amide bond formation. Moreover, the purposes of use of compounds of General Formula I in the citations is different from that of the present application.

Accordingly, the claimed subject matter is novel and involves inventive step in the light of prior-art documents **D2-D6** .

The claimed subjet matter has indsutrial applicability because of the purported uses thereof.

However, applications of these strategies are severely limited by the difficulties encountered in the acyl transfer step and/or the final auxiliary removal. Often the acyl transfer is very slow, or does not proceed at all.



Scheme 8

Reaction steps in the auxiliary strategies

It will be clearly understood that, although a number of prior art publications are referred to herein, this reference does not constitute an admission that any of these documents forms part of the common general knowledge in the art, in Australia or in any other country.

There are at least three requirements needed to make the auxiliary approach more versatile:

1. allow generic introduction of the auxiliary at the N atom,
2. allow more effective acylation of the nitrogen atom, and
3. allow removal of the auxiliary after acylation.

This combination of requirements severely limits the design of novel auxiliaries.

We have surprisingly found that a modification of the molecular fragment that links an oxygen or sulfur atom to the nitrogen atom has a strong accelerating effect on the acylation rate of the nitrogen atom, in contrast to prior art examples. In a particularly preferred embodiment, the modification further allows photolytic cleavage of the covalent bond between the acylated nitrogen atom and the remaining molecular fragment that connects the nitrogen atom with the oxygen or sulfur atom.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

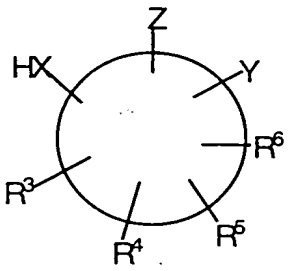
1. A method of

a) synthesis of a linear or cyclic peptide,

b) synthesis of a C-terminal modified peptide, or

c) on-resin cyclisation of a peptide molecule,

comprising the step of linking a cyclic aromatic or alkyl auxiliary compound of General Formula I to an amine nitrogen atom.



I

in which the ring optionally comprises one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulphur;

is of 5 to 7 atoms;

comprises 3 carbon atoms substituted respectively by XH, Z, and Y; and

is additionally substituted by groups R^3 and R^4 when the compound is a 5-membered ring, or is additionally substituted by groups R^3, R^4, and R^5 when the compound is a 6-membered ring, or is additionally substituted by groups R^3, R^4, R^5 and R^6 when the compound is a 7-membered ring,

in which

X is oxygen, sulphur, CH_2O-, or CH_2S-;

Y is an electron-withdrawing group;

Z is any group which allows the formation of a covalent carbon-nitrogen bond; and

R^3, R^4 and R^5 are each independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted

heteroaryl, alkoxy, aryloxy, XH or Y, or a covalent linkage to a solid support, and
in which R^3 and R^4, R^4 and R^5, or R^5 and R^6 can optionally together with the ring form a 5-, 6-, or 7-membered ring, thereby to facilitate conversion of the amine to an amide.

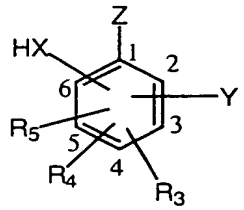
2. A method according to claim 1, in which Y is nitro, ketone, carboxylic ester, amide, nitrile, sulfonamide, sulfoxide, sulfone, sulfonate, fluoride, chloride, bromide or iodide.

3. A method according to claim 1 or claim 2, in which Z is an aldehyde, alkylalcohol, alkylhalide, or a ketone, or is a halogenated C_{1-3}alkyl group.

4. A method according to claim 3, in which the halogenated alkyl group is a methyl group.

5. A method according to claim 3 or claim 4, in which the halogen is iodine, bromine or chlorine.

6. A method according to any one of Claims 1 to 5, in which the auxiliary compound is of general Formula II



II

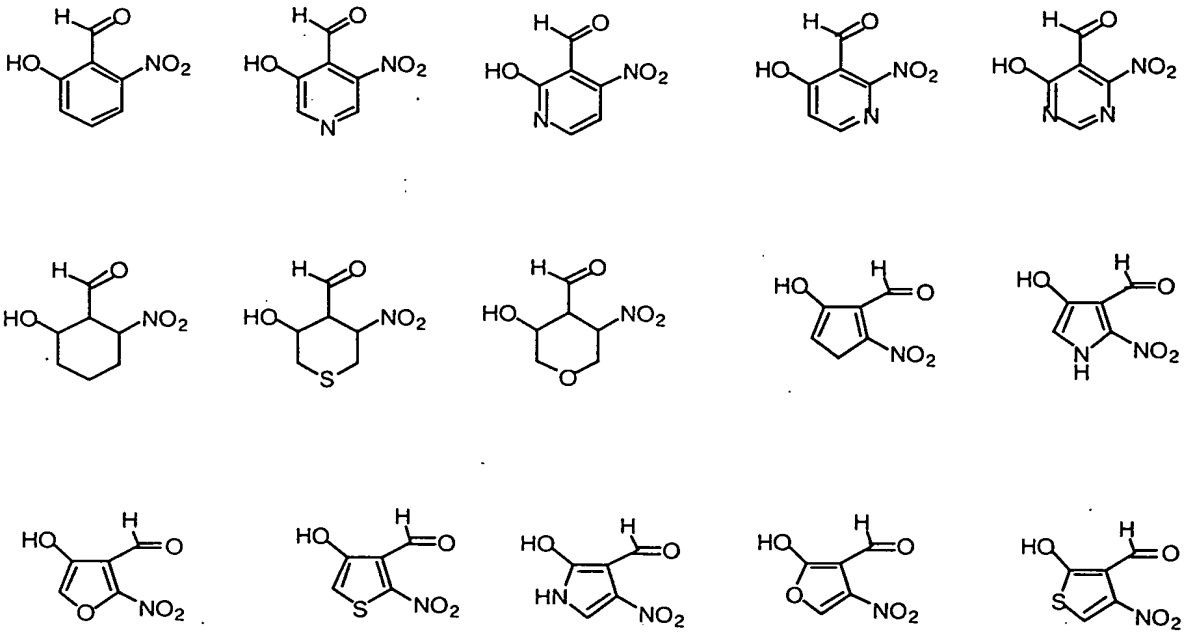
7. A method according to any one of claims 1 to 6, in which the XH group is at position 2 or 3 in General Formula I or General Formula II, and Y is at any other position.

8. A method according to claim 7, in which the XH group is at position 2.

9. A method according to any one of claims 1 to 8, in which Y is at position 6.

10. A method according to claim 9, in which Y is NO_2.

11. A method according to any one of claims 1 to 4, in which the auxiliary compound is selected from the group consisting of



comprising the step of linking a cyclic auxiliary compound of General Formula I, General Formula II, General Formula III, or General Formula IV to an amine nitrogen atom, thereby to facilitate conversion of the amine to an amide.

15. A method according to claim 14, in which XH in General Formula III is at position 2, and Y is NO_2 at position 6.

16. A method according to claim 1 or claim 15, in which R^3, R^4 , R^5 and R^6 are independently selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, and a covalent linkage to a solid support.

17. A method of synthesis of a cyclic peptide, comprising the steps of

a) synthesising a linear peptide to be cyclised,

b) linking an auxiliary compound as defined in any one of claims 1 to 11 to a desired primary amine of the linear peptide,

c) activating a desired carboxylic acid to effect cyclisation, and where necessary inducing ring contraction, and optionally

d) removing the auxiliary compound after complete N-acylation.

18. A method according to claim 17, in which ring contraction is induced by heating or by addition of a metal.

19. A method according to claim 17 or claim 18, in which the auxiliary compound is of General Formula III, and the auxiliary compound is removed by photolysis.

20. A method according to any one of claims 17 to 19, in which steps a) to d) are performed on a solid support,